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-It is noted that a certified English translation of Langhoff et al. (DE 19855426 A1, dated June 8, 2000) which was furnished to the applicant was incorrectly scanned and filed with Examiner's Answer mailed 11/16/2006 (see pages 16 to 26). It should have been separatly mailed and filed in IFW.
-No further commentary needed.
-Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.
Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

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PRIMARY EXAMINER

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SUBSTANCE FOR USE IN THE TREATMENT AND PROPHYLAXIS OF RHEUMATIC AND ARTHRITIC DISORDERS AND IN THE PROPHYLAXIS OF CARDIOVASCULAR DISORDERS

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SUBSTANCE FOR USE IN THE TREATMENT AND PROPHYLAXIS OF RHEUMATIC AND ARTHRITIC DISORDERS AND IN THE PROPHYLAXIS OF CARDIOVASCULAR DISORDERS

[Mittel zur Therapie und Prophylaxe von rheumatisch-arthritischen Erkrankungen und zur Prophylaxe von cardiovasculären Erkrankungen]

Inventors:	Same as Applicants
Applicants:	Wolfgang Langhoff and Udo Laumann

The following statements are taken [unedited] from the documents submitted by the applicant.

Description

/2*

The present invention relates to a pharmaceutical composition, in particular a substance for use in the treatment and prophylaxis of rheumatic and arthritic disorders, in particular of rheumatism and arthritis, and in the prophylaxis of cardiovascular (heart and circulation) disorders, in particular of cardiac infarction, atherosclerosis stenosis and thrombosis. The rheumatic and arthritic disorders and the cardiovascular disorders have underlying inflammatory processes in common.

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* [Numbers in the margin indicate pagination of the original foreign text.]

In our society, disorders of the locomotor system and of the cardiovascular system constitute a considerable portion of the cases requiring treatment. Thus, the economic damage due to days not worked because of illness or early retirement is high.

The disorders listed above are manifestations that are autoimmunologically and genetically predisposed and that accompany and/or are initiated by small inflammatory processes in the body.

It is known that the daily ingestion of ω-3-unsaturated (polyunsaturated) fatty acids is partially responsible for reducing the inflammatory processes. Therefore, it has been observed that the ingestion of ω-3-unsaturated fatty acids leads to an anti-inflammatory effect while at the same time other effects, e.g., effects detrimental to the gastric system, are observed, and on ingestion of NSAIDs (nonsteroidal anti-inflammatory drugs), are absent. Overall, this leads to an improved quality of life since fewer medicinal products can be administered and therefore fewer adverse events typically observed with medicinal products occur, such as can develop for example, on administration of medicinal products of the NSAID type.

The cardiovascular disorders, such as cardiac infarction, atherosclerosis and stenosis, are also triggered and reinforced by local inflammatory processes. Bacterial infiltration (e.g., Chlamydia) can further aggravate these processes. In most cases, the precursor of thrombosis is atherosclerosis. Acetylsalicylic acid, which is known to be a platelet aggregation inhibitor, is only a weak inhibitor of the platelet function as well as only a weak antithrombocytic substance. Normally, doses of 75-160 mg/day are used to inhibit aggregation.

It is known that acetylsalicylic acid in a concentration of approximately 75 mg per person and per day promotes the formation of the highly effective endogenous, intracellular radical catcher ferritin. Ferritin is known to be a cytoprotective antioxidative protein that catches free iron ions in the cellular metabolism and thereby counteracts the oxygen-dependent radical formation, which has the effect that inflammatory processes which invariably involve radicals are not further aggravated.

Thus, one problem to be solved by the present invention is to make available a pharmaceutical composition which is improved with respect to its effect in the treatment and prophylaxis of inflammatory processes in the body, in particular its effect in the treatment and prophylaxis of rheumatic and arthritic disorders and in the prophylaxis of cardiovascular disorders.

Specifically, the present invention relates to a pharmaceutical composition comprising

(a) a minimum of one ω-3-unsaturated fatty acid and/or its physiologically acceptable derivatives,

(b) vitamin E,

(c) vitamin C, and

(d) acetylsalicylic acid.

The ω-3-unsaturated fatty acid used is preferably α-linolenic acid. Preferably, the present invention relates to a pharmaceutical composition comprising

(a) 70-82 wt% of a minimum of one ω-3-unsaturated fatty acid, in particular α-linolenic acid, and/or its physiologically acceptable derivatives,

(b) 7.5-13 wt% of vitamin E,

(c) 10-15 wt% of vitamin C, and

(d) 0.5-2 wt% of acetylsalicylic acid,

relative to the composition comprising (a), (b), (c) and (d).

Surprisingly, it was found that in the treatment and prophylaxis of rheumatic and arthritic disorders and in the prophylaxis of cardiovascular disorders, the combination of the active substances (a) to (d) is considerably more effective than the separate principal substances ω-3-unsaturated fatty acid (and/or its physiologically acceptable derivatives), vitamin E, vitamin C and acetylsalicylic acid.

Since acetylsalicylic acid according to the present invention is used in extremely low doses, i.e., lower than 75 mg/day, preferably lower than 60 mg/day, a platelet aggregation inhibiting effect, if any, is barely noticeable. As a result, none of the known adverse effects of acetylsalicylic acid, such as gastric hemorrhages or pseudoallergic reactions, occur. No other known product is able to lead to the anti-inflammatory effect achieved with the composition according to the present invention in the treatment of rheumatic, arthritic and cardiovascular disorder with such few adverse effects.

The composition according to the present invention is intended for oral administration and can be used in the form of a powder, a tablet, a sugar-coated pill, a capsule, a solution, a concentrate, a syrup, a suspension, a gel or in the form of a dispersion.

The composition according to the present invention is dosed to ensure that the total quantity of acetylsalicylic acid (d) administered to the body is between 30 and 75 mg per day, preferably between 35 and 45 mg per day, and especially between 35 and 40 mg per day (for person with a body weight of approximately 75 kg). The quantitative content of components (a), (b) and (c) can be computed based on the percentages given for each component above. The composition according to the present invention can be administered in several separate doses distributed over the day. In addition, it is also possible to administer components (a) to (d) not only as a mixture but also separately. In such a case, the combination of active substances can be made available in such a way that the individual components are provided in separate form and can be either mixed prior to administration or can be administered separately (kit of parts). /3

The ω-3-unsaturated fatty acids can be used in pure form or in the form of their physiologically acceptable derivatives, in particular in the form of their esters. The

physiologically acceptable esters of the ω-3-unsaturated fatty acids preferably are their mono-, di- and triglycerides or their alkyl esters with 1-4 C atoms, in particular ethyl esters. The ω-3-unsaturated fatty acid and their derivatives preferably are metabolized in the body to form prostaglandins.

The ω-3-unsaturated fatty acids are selected especially from the group comprising α-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid or mixtures thereof. The ω-3-unsaturated fatty acids can be used not only in pure form but also, as already mentioned above, in the form of their physiologically acceptable synthetic or naturally occurring derivatives, in particular the glycerol esters or the alkyl esters with 1-4 C atoms. The source of the naturally occurring derivatives of the ω-3-unsaturated fatty acids, in particular of the triglycerides, especially worth mentioning includes above all wheat germ oil, soybean oil, walnut oil and rapeseed oil.

The source of α-linolenic acid especially worth mentioning includes above all hempseed oil (which contains approximately 25-30% of α-linolenic acid) and linseed oil (which contains approximately 35-70% of linolenic acid), the source of eicosapentaenoic acid and docosahexaenoic acid includes in particular fish oils or concentrates thereof. The naturally occurring sources contain the ω-3-unsaturated fatty acids or the derivatives thereof preferably in a quantity of at least 10%.

The fish oils to be used according to the present invention are in particular those that contain approximately 10-35% of eicosapentaenoic acid and docosahexaenoic acid each. The fish oils to be used are in particular cod liver oil and salmon oil and their concentrates. As a rule, it is possible to use all sources of ω-3-unsaturated fatty acids and their derivatives that the body converts into prostaglandins.

According to the present invention, at least one ω-3-unsaturated fatty acid in pure form or in the form of its physiologically acceptable derivatives is used; however, it is also possible to use mixtures of ω-3-unsaturated fatty acids or mixtures of ω-3-unsaturated fatty acids with their physiologically acceptable derivatives.

The composition according to the present invention contains 70-82 wt%, preferably 75-80 wt%, of the ω-3-unsaturated fatty acids, in particular α-linolenic acid or its physiologically acceptable natural or synthetic derivatives, especially of the esters mentioned above, relative to the composition comprising (a), (b), (c) and (d). If sources of ω-3-unsaturated fatty acids, e.g., the above-mentioned natural oils containing the triglycerides of the ω-3-unsaturated fatty acids are used, the quantities mentioned refer to the quantity of the source used.

Vitamin E is used in pure form. The composition according to the present invention contains 7.5-13 wt%, preferably 7.5-8.5 wt%, of vitamin E, relative to the composition comprising (a), (b), (c) and (d).

Vitamin C is used in pure form. The composition according to the present invention contains 10-15 wt%, preferably 12-15 wt%, of vitamin C, relative to the composition comprising (a), (b), (c) and (d).

Acetylsalicylic acid is used in pure form. The composition according to the present invention contains 0.5-2.0 wt%, preferably 0.5-1.5 wt%, of acetylsalicylic acid, relative to the composition comprising (a), (b), (c) and (d). Acetylsalicylic acid is preferably used in the form of an enteric coated formulation, i.e., a formulation that does not release the active substance in the stomach but in the small intestine instead, e.g., in the form of a conventional microencapsulated dosage known from the prior art.

Furthermore, the composition according to the present invention may, additionally and independently of one another, also contain physiologically acceptable quantities of coenzyme Q, beta-carotene, biologically active selenium, one or more water-soluble vitamins, physiologically valuable elements, garlic and/or hawthorn extract, and components that are commonly used in the formulation (galenic pharmacy).

Merely by way of an example, it should be mentioned that the composition according to the present invention, relative to 100 parts by weight of the composition comprising (a), (b), (c) and (d), may additionally contain:

- 0.1-0.5 parts by weight, preferably 0.2-0.4 parts by weight, of coenzyme Q;
- 0.1-0.4 parts by weight, preferably 0.2-0.3 parts by weight, of beta-carotene;
- 6×10^{-4} to 8×10^{-4} parts by weight, preferably 6.5×10^{-4} to 7.5×10^{-4}, parts by weight of biologically active selenium;
- one or more of the water-soluble vitamins thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, biotin, cobalamin and folic acid, in particular in the parts by weight listed in the table* below.

*[In tables, equations, and figures, commas in numbers denote decimal points.]

(1) Vitamine	(2) von	(3) bis	(4) bevorzugt von	(5) bevorzugt bis
(6) Thiamin	0,01	0,1	0,02	0,09
(7) Riboflavin	0,01	0,1	0,02	0,09
(8) Niacin	0,1	1,0	0,2	0,9
(9) Pyridoxin	0,01	0,1	0,02	0,09
(10) Panthotensäure	0,05	0,5	0,1	0,4
(11) Biotin	$3*10^{-3}$	$6*10^{-3}$	$4*10^{-3}$	$5*10^{-3}$
(12) Cobalamin	$1*10^{-4}$	$4*10^{-4}$	$2*10^{-4}$	$3*10^{-4}$
(13) Folsäure	$1*10^{-2}$	$4*10^{-2}$	$2*10^{-2}$	$3*10^{-2}$

Key: 1 Vitamins
2 From
3 To
4 Preferably from
5 Preferably to
6 Thiamine
7 Riboflavin
8 Niacin
9 Pyridoxine
10 Pantothenic acid
11 Biotin
12 Cobalamin
13 Folic acid

- one or more of the elements in their physiologically acceptable form, selected from the group comprising magnesium, iron, copper, iodine, manganese, zinc, molybdenum and chromium, in particular in the parts by weight listed in the table below:

① Element	② von	③ bis	④ bevorzugt von	⑤ bevorzugt bis
Mg	0,01	0,1	0,02	0,09
Fe	0,01	0,02	0,015	0,017
Cu	$1,0*10^{-3}$	$2*10^{-3}$	$1,1*10^{-3}$	$1,9*10^{-3}$
I	$2*10^{-4}$	$3*10^{-4}$	$2,2*10^{-4}$	$2,8*10^{-4}$
Mn	$3*10^{-3}$	$4*10^{-3}$	$3,2*10^{-3}$	$3,8*10^{-3}$
Zn	0,01	0,02	0,011	0,019
Mo	$1*10^{-4}$	$2*10^{-4}$	$1,1*10^{-4}$	$1,9*10^{-4}$
Cr	$1*10^{-4}$	$2*10^{-4}$	$1,1*10^{-4}$	$1,9*10^{-4}$

Key: 1 Element
2 From
3 To
4 Preferably from
5 Preferably to

- and other conventionally used components, such as antioxidants, dispersing and/or suspending substances and additional aids commonly used in galenic pharmacy, such as flavoring substances, dyes, thickening substances and conventionally used physiologically safe separating substances.

Relative to 100 parts by weight of the overall composition comprising (a), (b), (c) and (d), the composition according to the present invention may also contain

- 0.1-0.5 parts by weight, preferably 0.2-0.4 parts by weight, of garlic extract,
- 0.1-0.5 parts by weight, preferably 0.2-0.4 parts by weight, of hawthorn extract, or
- 0.1-1.0 part by weight, preferably 0.2-0.9 parts by weight, of combinations of garlic and hawthorn extract.

The pharmaceutical composition described above is suitable for use in the prophylaxis and/or treatment of inflammations in the human or animal body. In particular, the composition according to the present invention is suitable for use in the prophylaxis and treatment of rheumatic and arthritic disorders and in the prophylaxis of cardiovascular disorders. The rheumatic and arthritic disorders include, in particular, rheumatism and arthritis, and the cardiovascular (heart and circulation) disorders include, in particular, cardiac infarction, atherosclerosis, stenosis and thrombosis. Atherosclerosis is a precursor of thrombosis.

The composition according to the present invention can be used in methods for the preparation of medicinal products in which this composition is used to treat and/or prevent the disorders mentioned above and can subsequently be used in the doses mentioned above.

In connection with the composition according to the present invention, it was surprisingly found that the combination of ω-3-unsaturated fatty acids, or their physiologically acceptable derivatives mentioned above, vitamin E and vitamin C with acetylsalicylic acid, said acetylsalicylic acid overall being used in a very low dose, leads to an effect that enhances the anti-inflammatory action, i.e., to a synergistic effect. The administration of a combination of ω-3-unsaturated fatty acids (and/or their derivatives mentioned above), vitamin E, vitamin C and acetylsalicylic acid leads to a superior anti-inflammatory effect when compared to the administration of ω-3-unsaturated fatty acids (or their derivatives mentioned above), vitamin E, vitamin C or acetylsalicylic acid in the form of separate components. Thus, the compositions according to the present invention are especially suitable as substances for use in the treatment and therapy of rheumatic and arthritic disorders and for use in the prophylaxis of cardiovascular disorders.

The present invention will be illustrated in greater detail based on the examples below, without intending to restrict the invention in any way.

Example /5

In the example below, cod liver oil, vitamin E, vitamin C and acetylsalicylic acid, each in commercially available pure form, were used. An experiment in which linseed oil was used as the source for the ω-3-unsaturated fatty acid (α-linolenic acid) led to identical results.

In the test, the anti-inflammatory effect of the following formulations was compared after administration to a person (body weight approximately 75 kg) suffering primarily from a rheumatic and/or arthritic disorder as well as from a mild cardiovascular disorder:

A) 10 g of cod liver oil,
1000 mg of vitamin E, and
1000 mg of vitamin C,

B) 80 mg of acetylsalicylic acid,

C) 250 mg of vitamin E and
40 mg of acetylsalicylic acid,

D) 50% of A and 50% of B).

The overall amount listed above was administered daily, optionally in single doses, over a period of 14 weeks. Using a rating scale (1 = excellent, 2 = good, 3 = satisfactory, 4 = adequate, 5 = barely noticeable improvement, 6 = no improvement), the test subject described the effect of the above compositions as follows:

① Zusammensetzung	Bewertung ②
A	2
B	6
C	3
D	1

Key: 1 Composition
2 Rating

It was found that the oral administration of composition A), B) or C) by itself was less effective (led to a lesser improvement) than the administration of D). After the administration of composition D) according to the present invention, it was possible to observe a synergistic effect which exceeds the effect to be expected. The combination of A) and B), which constitutes composition D), is considerably improved when compared to the single components A), B) or C) used in the same quantity.

Claims

1. A pharmaceutical composition comprising

(a) a minimum of one ω-3-unsaturated fatty acid and/or its physiologically acceptable derivatives,

(b) vitamin E,

(c) vitamin C, and

(d) acetylsalicylic acid.

2. The composition as in Claim 1, characterized in that the composition contains

(a) 70-82 wt% of ω-3-unsaturated fatty acids and/or their physiologically acceptable derivatives,

(b) 7.5-13 wt% of vitamin E,

(c) 10-15 wt% of vitamin C, and

(d) 0.5-2 wt% of acetylsalicylic acid,

relative to the composition comprising (a), (b), (c) and (d).

3. The composition as in Claim 1 or 2, characterized in that the ω-3-unsaturated fatty acids are used in pure form, in the form of their mono-, di- or triglycerides, or in the form of their alkyl esters with 1-4 C atoms.

4. The composition as in Claim 1, characterized in that the ω-3-unsaturated fatty acid is selected from the group comprising α-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid or mixtures thereof.

5. The composition as in any one of Claims 1-4, characterized in that it contains the ω-3-unsaturated fatty acid in the form of its triglycerides as contained in linseed oil, hempseed oil, wheat germ oil, soybean oil, walnut oil, rapeseed oil, fish oil or mixtures thereof.

6. The composition as in Claim 5, characterized in that the fish oil is selected from the group comprising salmon oil and cod liver oil.

7. The composition as in any one of Claims 1-6, characterized in that, in addition, the composition also contains coenzyme Q, beta-carotene, biologically active selenium, one or more water-soluble vitamins, or mixtures of these components.

8. The composition as in any one of Claims 1-7, characterized in that, in addition, it also contains garlic extract and/or hawthorn extract.

9. The composition as in Claim 8, characterized in that the total quantity of garlic extract and/or hawthorn extract in the pharmaceutical composition measures 0.1-1.0 part by weight, relative to 100 parts by weight of the composition comprising (a), (b), (c) and (d).

10. The composition as in any one of Claims 1-9, characterized in that, in addition, it also contains beta-carotene, folic acid and biologically active selenium. /6

11. The composition as in Claim 10, characterized in that, relative to 100 parts by weight of (a), (b), (c) and (d), it contains

0.1 to 0.5 parts by weight of beta-carotene,

1×10^{-2} to 4×10^{-2} parts by weight of folic acid, and

6×10^{-4} to 8×10^{-4} parts by weight of biologically active selenium.

12. The composition as in any one of Claims 1-11, characterized in that it can be administered in a dose of 30-75 mg of acetylsalicylic acid per person and per day.

13. A substance comprising the composition as in any one of Claims 1-12 for use in the treatment of inflammations in the human or animal body.

14. The substance as in Claim 13 for use in the treatment and prophylaxis of rheumatic and arthritic disorders or in the prophylaxis of cardiovascular disorders.

15. The substance as in Claim 14 for use in the treatment and prophylaxis of rheumatism and arthritis and in the prophylaxis of cardiac infarction, atherosclerosis, stenosis and/or thrombosis.

16. The use of the composition as defined in any one of Claims 1-12 for use in the treatment of inflammatory disorders of the human or animal body.

17. The use as in Claim 16 for use in the treatment and prophylaxis of rheumatic and arthritic disorders and/or in the prophylaxis of cardiovascular disorders.

18. The use as in Claim 17 for use in the treatment and prophylaxis of rheumatism and arthritis and in the prophylaxis of cardiac infarction, atherosclerosis, stenosis and thrombosis.

19. The use as in any one of Claims 16-18 in a dose of 30-75 mg of acetylsalicylic acid per person and per day.

20. The use of the composition as defined in any one of Claims 1-12 for use in the production of a medicinal product for use in the treatment and/or prophylaxis of cardiovascular disorders.